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SUMMARY

This was a GMP/pre-approval inspection of the packaging facility/location conducted per 7456.002B "Drug Repackagers and Relabelers"; CP7356.021 "Drug Quality Reporting System – DQRS", and FACTS assignment #4741657. This location serves as the packager for Caraco Pharmaceutical Laboratories, LTD whose manufacturing facility and headquarters are located in Detroit, MI. All finished pharmaceuticals manufactured at Caraco's Detroit, MI facility are transported to this Farmington Hills, MI facility for finished packaging. In addition, products manufactured by (b) (4) [redacted] located in (b) (4) [redacted] are finished packaged at this facility.

There were (b) (6) EES pre-approval assignments associated with this packaging facility including: ANDA (b) (4) [redacted] (b) (4) [redacted] – Applicant Caraco Pharm.

ANDA (b) (4) – (b) (4) (b) (4) – applicant Caraco
ANDA (b) (4) – Pantoprazole Sodium 20 mg and 40 mg tablets – applicant (b) (4)
ANDA (b) (4) – Gabapentin 100 mg, 300 mg, 400 mg capsules – applicant (b) (4)
ANDA (b) (4) – applicant (b) (4)
The EES assignments for the above are attached as Attachments 1-5.

The inspection revealed numerous instances of inadequate line clearance/clean-up resulting in foreign tablets noted in the packaging equipment/room subsequent to the packaging of another drug product; failure to follow SOP calling for trending of the numerous (b) (4) inspection activities accomplished in 2008; failure to include complete information in the packaging records; failure to document cleaning activities in the use, cleaning and maintenance logs; and failure to maintain a use, cleaning, and maintenance log for all packaging equipment. Mr. Robert Kurkiewicz, Senior Vice President, Regulatory Affairs stated they would respond in writing.

The previous inspection at this facility yielded no 483 observations, but did yield discussions with management concerning manual addition of tablets to bottles and calculation of percentage yield documented in the packaging records. Corrections were promised by management and these corrections were confirmed during the current inspection.

ADMINISTRATIVE DATA

Inspected firm:	Caraco Pharmaceutical Laboratories, LTD.
Location:	24700 Crestview Ct Farmington Hills, MI 48335-1506
Phone:	248-474-5511
FAX:	
Mailing address:	
Dates of inspection:	12/11/2008, 12/12/2008, 12/15/2008, 12/16/2008, 12/22/2008
Days in the facility:	5
Participants:	Patsy J Domingo, Investigator Jonathan R. Loving, Investigator Adam J. Wilson, Investigator

HISTORY

Caraco Pharmaceutical Laboratories is a limited liability corporation headquartered in Detroit. The firm manufactures various drug products at its Detroit facility and conducts packaging operations in Farmington Hills which was acquired from (b) (4) in 2006. The history of this facility has not been changed since the last inspection conducted on 3/08.

Currently Caraco employs (b) (4) employees, (b) (4) employees for a total of (b) (4) including QA and managers at this facility which is a substantial increase since May 2008. Operations run Monday through Friday and (b) (4) There are (b) (4) during the business week with (b) (4) periods reported and staffed as follows: (b) (4) . This facility has reduced the number of lines it uses to package products from (b) (4) since the last inspection.

The previous inspection of this firm did not result in the issuance of an FDA-483, List of Observations; however, two verbal concerns were conveyed to management during the closeout discussion related to the practice of hand filling bottles during packaging and also not properly documenting the percentages of actual and theoretical yield for product at the conclusion of its packaging run. Corrective actions to each of the above listed verbal concerns were verified during this inspection (See Voluntary Corrections).

INTERSTATE COMMERCE

All distribution of products packaged at this facility are handled by personnel operating out of the Detroit, MI facility and the Wixom, MI facility. Finished packaged drug products are shipped from this facility to the Wixom, MI distribution center.

JURISDICTION

See EIR for Caraco's Detroit, MI facility.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

On 12/11/08 our credentials were shown and form FDA-482 was issued to Michael R. Lechman, Senior Packaging Manager who is the most responsible individual on a day to day basis at this facility. Mr. Lechman reports to Robert C. Wood, Associate Director Manufacturing who reports to Kaushik Gandhi, Vice President Manufacturing who reports to Daniel H. Movens, Chief Executive Officer.

Akin-Remi Ajac-Ayodele, Director Quality Special Projects who traveled in from Detroit upon our arrival, is the most responsible person representing the Quality Unit. Mr. Ajac-Ayodele (Remi) participated in the inspection and answered most of the quality related questions and described the various quality changes Caraco has implemented since the May 2008 inspection of the Detroit facility. (b) (6) who is the Sr. Quality representative at this location on a day to day basis was on vacation for the inspection but was present during the close-out meeting. Others involved with the inspection included:

Robert Kurkiewicz, Senior VP, Regulatory Affairs

Robert C. Wood, Associate Director of Manufacturing

Matt Marken, Senior QA Supervisor

Raj Subudhi, Packaging Manager

MANUFACTURING/DESIGN OPERATIONS

This packaging and product inspection facility is an extension/continuation of the processes begun at the Detroit, MI facility. If a batch has a deviation registered against it, and part of the corrective action involves inspection of the batch, those activities take place at this Farmington Hills facility under direction of a special processing operation (SPO) order initiated by Quality Assurance. Many of the batches produced at the alternative manufacturing sites located in India must be inspected by personnel at this facility before they are packaged, again under an SPO ordered by QA.

Caraco has renamed their packaging lines as follows: Lines (b) (4) Line , Room Area , Room Area was last used on 12/11/08 (the first day of our inspection) and was put out of service that same day. Blueprints obtained at last inspection did not label Area as a processing area. During our inspection, several rooms were being reconstructed and were out of use.

During this inspection we selected a number of packaging records to review. Five records requested were taken from the shipping log representing lots that had just been completed and shipped to the Wixom warehouse to await release and shipping: Paroxetine lot (b) (4) Glipyzide lot (b) (4) Amlodipine Beyslate lot (b) (4) Metformin lot (b) (4) and Metoprolol lot (b) (4) From the SPO listing we requested (**Exhibits Pjd-1/15**) we selected a number of packaging records with an SPO associated to it for review. These include the following:

- Digoxin tabs lot (b) (4) inspected for the presence of thick or thin tablets
- Midrin Caps lot (b) (4) inspected for damaged capsules
- Zolpidem Tartrate lot (b) (4) inspected for the presence of black spots
- Amlodipine Beyslate Tablets lot (b) (4) bulk converted 500 count to a 90 count under SPO (b) (4). No concerns noted.
- Paroxetine tablets lot (b) (4) bulk converted 90 count bottles to 30 count bottles under SPO (b) (4). No concerns noted.

- Metoprolol Tartrate Tablets lot (b) (4) inspected under SPO # (b) (4) dated 5/5/08 for the presence of foreign tablets found during packaging in the filling machine. The type of foreign tablet was undetermined.
- Metoprolol Tartrate Tablets lot (b) (4) inspected under SPO (b) (4) dated 5/3/08 for the presence of foreign tablets. Root cause was attributed to an issue with the coating process in manufacturing.
- Metoprolol Tartrate Tablets lot (b) (4) inspected under SPO (b) (4) dated 10/2/08 for the presence of plastic parts. This inspection was initiated due to problems found in another lot, (b) (4). There were clerical errors observed in the SPO record related to it referencing the wrong incident track sheet. A copy was obtained of the memo issued on 12/16/08 from Varkey Varughese documenting the correct IR number that should have been referenced in the SPO. Mr. Ajac-Ayodele said this memo would be added to the packaging records to correct the problem.
- Digoxin Tablets lot (b) (4) inspected for the presence of metal parts. This problem was the result of manufacturing issues and not pertinent to the current packaging inspection.
- Metoprolol Tartrate lot (b) (4) inspected under SPO (b) (4) for the presence of different strength version of product. The investigation report determined the root cause was due to a manufacturing error.

Additional records reviewed are discussed in the Inspectional Conditions and Management's Response section of this report.

MANUFACTURING CODES

Bulk product is received from the Detroit, MI or (b) (4). The packaged product is identified with the bulk lot number (b) (4) or '(b) (4) for (b) (4) Industries (India)) with a letter suffix added. (b) (4)

COMPLAINTS

The following complaints were reviewed:

- (b) (4) involving Mirtazapine 45 mg lot 80560A dated 4/22/08 found a 15 mg tablet in the bottle determined to be related to operations at the Detroit location;

- (b) (4) involving Clonazepam Tablets lot (b) (4) inspected for the presence of soft, thin, broken tablets as described in SPO (b) (4) and Rejected Tablet Evaluation (**Exhibits Pjd-184/185**). This lot was later the subject of a complaint from a pharmacist who found the tablets to be different sizes. Complaint (b) (4) dated 9/30/08 (**Exhibits Pjd-186-214**) was the only complaint received for this lot. Caraco evaluated the tablets returned by the

complainant and determined the tablets were within USP specifications for thickness and weight. (**see Exhibits Pjd-213**).

- (b) (4) the (b) (4) complaint received for Zolpidem Tartrate 10 mg lot 80311A (**Exhibits Pjd-146-182**). Refer to FDA-483 inspectional observation #3.b.

RECALL PROCEDURES

Any recalls would be handled by Caraco's Detroit location.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Observations listed on form FDA 483

OBSERVATION 1

Inspection of the packaging facilities immediately before use is not done to assure that all drug products have been removed from previous operations.

There have been numerous instances, 5/2008 through the present, where the failure to perform an adequate cleaning procedure ((b) (4) has resulted in the necessity to conduct (b) (4) inspection of packaged finished product lots for the presence of foreign tablets noted to be present in/on/near the packaging equipment after Quality Assurance release of the equipment/room for use. Examples include:

a. Meloxicam Tablet lot (b) (4) inspected under SPO # (b) (4) dated 5/1/08 for the presence of Carvedilol 25 mg

b. Metformin HCl Tablet lot (b) (4) inspected under SPO # (b) (4) dated 8/7/08 for the presence of Mirtazapine 45 mg

c. Metformin HCl Tablet lot (b) (4) inspected under SPO (b) (4) dated 8/21/08 for the presence of Metoprolol Tartrate 100 mg

d. Tramadol HCl tablet lot (b) (4) inspected under SPO # (b) (4) dated 8/24/08 for the presence of Metoprolol Tartrate 50 mg tablets

e. Methimazole Tablets lot (b) (4) inspected under SPO (b) (4) dated 9/6/08 for the presence of Clonazepam 0.5 mg tablets

f. Metformin HCl tablet lot (b) (4) inspected under SPO # (b) (4) dated 10/20/08 for the presence of Metoprolol Tartrate 100 mg tablets

g. Tramadol HCl Tablets lot (b) (4) inspected under SPO (b) (4) dated 11/3/08 for the presence of Atenolol Tablets 25 mg

h. Zolpidem Tartrate Tablets lot (b) (4) inspected under SOP (b) (4) dated 11/18/08 for the presence of Carbamazepine Tablets 100 mg

i. Metformin HCl Tablets lo (b) (4) inspected under SPO (b) (4) dated 9/4//08 for the presence of Metoprolol Tartrate 100 mg

Reference: 21 CFR 211.130(e)

Supporting Evidence and Relevance:

Review of the Special Processing Operation (SPO) Log for 2007/2008 (**Exhibits Pjd-1/15**) revealed (b) (4) instances where the reason for the SPO to be issued had to do with foreign tablets. (b) (4) of these instances were pulled for our review.

1.A.

Special Processing Operation (b) (4) (**Exhibit Pjd- 32**) was initiated 5/1/08 for the inspection of Meloxicam Tablets 7.5 mg lot (b) (4) following the investigation, under IR (b) (4) (**Exhibits Pjd-33/34**) after a packaging employee noted a partial tablet, white in color (not Meloxicam which is yellow) wedged inside the packaging equipment. Packaging was stopped and the channel counter was dismantled for additional cleaning during which additional tablet parts were discovered.

Packaging of Meloxicam Tablets lot (b) (4) (**Exhibits Pjd-22/26**) began 4/30/08 on Packaging Line (b) (4) and (b) (4) cases had been completed when this foreign tablet incident was noted (**Exhibit Pjd-27**). The Line- (b) (4) room log (**Exhibit Pjd-35**) documents Carvedilol 25 mg Tablet lot 80801A was the lot packaged on Line (b) (4) previous to Meloxicam lot (b) (4) It also documents that a (b) (4) cleaning occurred on 4/30/08 just prior to bringing Meloxicam lot (b) (4) into the room.

Inspection of the (b) (4) cases was accomplished 5/1/08 under SPO # (b) (4).

The Statement of Contributory/Root Cause as documented in the Incident Report, IR (b) (4) (**Exhibit Pjd-33/34**) was the operator did not perform a thorough cleaning and both the Supervisor/Assistant Manager-Packaging who performed the checking and the QA Inspector who verified the cleaning failed to note the foreign tablet particles.

The Risk Analysis/Impact Statement documented in the incident report states "(b) (4) [redacted]."

1.B. (AJW)

Review of Metformin HCl 500 mg tablet Lot (b) (4) packaging record shows an SPO (Special Processing Order) (**Exhibit AJW 105**) was executed due to foreign tablet contamination. The associated incident tracking sheet, IR (b) (4), states "(b) (4) [redacted]" (**Exhibit AJW 107**). The SPO, (b) (4), called for a (b) (4) inspection. The investigation report (**Exhibit AJW 109-110**) for this incident revealed

the foreign tablet, identified as Mirtazapine 45mg , had been packaged directly prior to lot (b) (4) on the same line. A (b) (4) cleaning was conducted between these batches (**Exhibit AJW-109**).

1.C. (AJW)

Metformin HCl Tablet, USP, 1000 mg Lot (b) (4) packaging record (**Exhibit AJW 1-57**) was reviewed due to a foreign tablet found during packaging. According to Incident Tracking Sheet # (b) (4) (**Exhibit AJW 58**) initiated for this deviation, the foreign tablet was identified as being from a Metoprolol Tartrate batch packaged four lots prior (see Packaging Line (b) (4) log attached as **Exhibits AJW 86, 87**). The line log documents that in the interim, Metformin lots (b) (4) , (b) (4) and (b) (4) were packaged on this line and the line was subjected to one (b) (4) cleaning as well as three (b) (4) cleanings. Lot (b) (4) was (b) (4) inspected under SPO (b) (4) (**Exhibit AJW 85**) as it had not been released. Lots (b) (4) and (b) (4) were released to market by the time this issue was discovered as documented on their respective Packaging Record batch review pages attached as (**Exhibits AJW 81-84**). As a result, no action was taken other than checking the retain samples which consisted of three 1000-count bottles for each lot as documented in the Investigation Report for IR (b) (4) attached as **Exhibit AJW 61.** The Risk analysis section for this Incident Report addresses the two batches that were (b) (4) inspected, but not the two batches that were already on the market (**Exhibit AJW 61**). Additionally, the (b) (4) packaging record contained no indication of any investigation/deviation related to its processing.

1.D.

Special Processing Operation # (b) (4) (**Exhibit Pjd-89**) was initiated 08/24/08 for the inspection of Tramadol HCl 50 mg tablet lot (b) (4) following the investigation, under IR (b) (4) (**Exhibits Pjd-85/88**) initiated after two packaging employees noted two foreign tablets, one in each of two different locations, in packaging line/room (b) (4) sometime after the packaging of this Tramadol lot had started.

Packaging Line # (b) (4) was checked and approved for packaging Tramadol lot (b) (4) on 8/23/08 as documented in the Line (b) (use log (**Exhibit Pjd-99**). Metoprolol Tartrate lot (b) (4) had been the previous lot packaged on this line. Packaging of began the morning of 8/24/08 with the first checks occurring at approximately 7:00 am as documented on the In Process Inspection Report attached as **Exhibit Pjd-96**. Production was stopped at 9:40 after the foreign tablets were discovered.

Inspection of the (b) (4) cases was accomplished on 8/24/08 under SPO (b) (4) (**Exhibit Pjd-89**). The Statement of Contributory/Root Cause as documented in the Investigation Report for Incident #IR-(b) (4) (**Exhibit Pjd-88**) was documented as the operator failed to properly perform the (b) (4)

cleaning of the packaging line and the QA Inspector and Production Supervisor failed to properly inspect the packaging line.

The Risk Analysis/Impact Statement documented in the investigation report (**Exhibit Pjd-87**) states "(b) (4) ."

1.E. (JRL)

Caraco's distribution facility in Wixom initiated incident tracking record, IR(b) (4) (**Exhibit #JRL 1**), for Methimazole Tablets lot#(b) (4) The incident was in response to yellow Clonazepam tablets found mixed in the Methimazole scrap bag. The foreign tablets discovered were from a lot directly preceding the packaging of the Methimazole (**Exhibit #JRL 2**). The course of events that led to the discovery and subsequent inspection and investigation of the foreign tablets were unclear. Review of the deviation record states "(b) (4) . . ." on 8/29/08 at Caraco Wixom, however, IR(b) (4) documents the foreign tablet being discovered nine days after the completion of the packaging process on 8/20. Caraco's internal investigative report determined that discovery took place earlier (**Exhibit #JRL 3-4**):

(b) (4) . . .

Akin-Remi Ajac-Ayodele, Director of Quality Special Projects, said he believes the investigation report was inaccurate and maintains that discovery was made by QA at Wixom. Mr. Ajac-Ayodele suggested that the cleaning operator was not aware of the foreign tablet when it was swept into the scrap bag. A conference call with the authors of the investigation report, (b) (6) , Quality Engineer and Leonard Louis, Manager of Quality Engineering, confirmed that discovery was indeed made during the clean up process. A(b) (4) clean followed the packaging of Methimazole lot and was documented in the maintenance use and cleaning record on 8/20 at 5:05pm. There was no record of the foreign tablet discovery at the time it occurred.

On the day the incident was documented in IR(b) (4), an email was sent by Gerared Fielder, Manager of Quality Assurance – Farmington Hills, to(b) (6) , Senior QA Inspector - Wixom, stating that Mr. Fielder was not made aware of the issue until the discovery at Wixom (**Exhibit #JRL 5-6**). Wixom pulled back the stock of the product and placed a QA hold on the affected lot. The lot was then shipped back to Farmington and underwent a(b) (4) inspection per SPC(b) (4) on 9/6/08 (**Exhibit #JRL 7**). Findings of that inspection yielded that the lot did not contain any other foreign Clonazepam tablets.

The investigation into the root cause of the foreign tablet resulted in the following corrective action: The operator and line supervisor were retrained in (b) (4) cleaning procedures. There was no action taken with respect to documenting a deviation event at the time of occurrence (Reference: 21 CFR 211.100(b)).

1.F.

Special Processing Operation #(b) (4) (**Exhibit Pjd-109**) was issued 10/14/08 for the inspection of Metformin HCl 500 mg lot (b) (4) following the investigation under IR (b) (4) (**Exhibits Pjd-106-108**) after a packaging employee noted a foreign tablet, identified as Metoprolol Tartrate, on the slat counter. This foreign tablet was noted during the (b) (4) cleaning of Line (b) (4) performed after completing the packaging of Metformin lot (b) (4) The investigation (**Exhibits Pjd-113/114**) concluded Metoprolol Tartrate was packaged just prior to this lot of Metformin. It also documented that based on the short ((b) (4)) cleaning time recorded for the (b) (4) cleaning (a total dismantling of the line and wash of the various equipment parts) that a thorough cleaning was not performed.

The Risk analysis/Impact Statement (**Exhibit Pjd-114**) states '(b) (4) [redacted] ."

1.G. (JRL)

Product lot# (b) (4) Tramadol HCL tablets, was issued incident record IR-(b) (4) due to a foreign tablet being discovered in the channel counter during the product packaging process (**Exhibit #JRL 8**). The incident resulted in a (b) (4) inspection under SPO (b) (4) on 11/3/08. Caraco's internal investigation yielded the foreign tablet was Atenolol 25mg which preceded the Tramadol lot on packaging line (b) (4) **Exhibit #JRL 9**). The root cause appears to be the result of the Atenolol falling in an area of the channel counter that is hidden from view. The company took corrective action by issuing a memo that calls for the re-training of their packaging and QA personnel to include this spot in their (b) (4) cleanings.

1.H.

Special Processing Operation #(b) (4) (**Exhibit Pjd-116**) was initiated 11/23/08 for the inspection of Zolpidem Tartrate 10 mg lot (b) (4) following the investigation under Incident #(b) (4) (**Exhibits Pjd-117/127**) after a packaging employee found five Carbamazepine tablets in the packaging equipment. Again the investigation concluded an incomplete cleaning operation was performed and the check performed by the Supervisor and QA Inspector was not proper as well (**Exhibit Pjd-120**).

Again (b) (4) inspection of the affected lot was performed and the stated risk analysis was '(b) (4) ".

1.I. (AJW)
Special Processing Operation (b) (4) (**Exhibit AJW-85**) documents the (b) (4) inspection of Metformin HCl 1000 mg tablet lot for the presence of foreign tablets on 12/2-3/08.

Discussion with Management:

Mr. Ajac-Ayodele acknowledged that the cleaning process between lots was an issue and stated that one of the measures recently implemented was a mandatory '(b) (4) clean between lots of the same product but different strengths. Robert Kurkiewicz, Senior VP of Regulatory Affairs stated the firm would issue its formal response in writing at a later date.

OBSERVATION 2

The responsibilities and procedures applicable to the quality control unit are not fully followed.

SOP (b) (4) (SPO's) stated purpose includes "(b) (4) ". Section (b) (4) of this SOP calls for "(b) (4) ". It was determined that there has been no trending of SPO's issued for 2008, although (b) (4) SPO's have been issued in 2008 as of the start of this inspection. The following is a partial summary of the reasons for SPO issuance for 2008 as listed in the database provided:

Foreign Tablets	(b) (4) instances ((b) (4) since May 2008)
Thick/Thin Tablets	(b) (4) instances ((b) (4) Thick) - (b) (of which were for Clonazepam
Foreign Contamination	(b) (4) instances ((b) (4) since September)
Inspection of (b) (4) " lots from (b) (4) n	(b) (4) instances
Inspection of "(b) (4) lots from (b) (4)	(b) (instances
Inspection (non discript)	(b) (4) instances (b) (4) since 6/27/08)

Reference: 21 CFR 211.22(d)

Supporting Evidence and Relevance:
The SOP covering Special Processing Operations states on page 2 (**Exhibit Pjd-17**) under section (b) (4) that the Senior Manager, Quality Assurance or designee is responsible for "(b) (4) ". When I requested the trending for the (b) (4) SOP's documented in the (b) (4) " (**Exhibit Pjd-4/15**) I was told by Mr. Ajac-Ayodele that this was only performed annually.

Discussion with Management:

Mr. Ajac-Ayodele indicated they would be implementing (b) (4), and possibly continuous, trending of SPO events.

OBSERVATION 3

Batch production and control records do not include complete information relating to the production and control of each batch.

a. On 12/11/08 we observed a problem that occurred during packaging of Zolpidem Tartrate Tablet lot (b) (4) where, due to an alignment issue bottles were shorted tablets as the tablets were observed to be spilling onto the floor. The line had to be stopped, adjustments made, and bottles removed and their contents dumped. Review of the packaging record following the completion of the run revealed no notation of the problems we witnessed.

b. Review of the batch record for Zolpidem Tartrate Tablet lot 80311A reveals no indication of a problem during packaging. However, review of Caraco's complaint data base reveals there have been (b) (4) complaints of incorrect tablet count received for lot 80311A.

Reference: 21 CFR 211.188

Supporting Evidence and Relevance:
3.a.
Attached as **Exhibits Pjd-128/134** is the packaging record for Zolpidem Tartrate Tablets, 5 mg lot (b) (4) packaged in 1000 count bottles. Six of the seven pages for this record contain a section at

the bottom of the page for "Comments". This record contains no indication of the problems we observed during our visit to Packaging Line [redacted] the morning of 2/11/08.

3.b.

Attached as **Exhibits Pjd-135/145** is the packaging record for Zolpidem Tartrate Tablets, 10 mg lot 80311A packaged in 100 count bottles. Review of this batch record finds the only comments recorded were "wrong time entered", "wrong entry", or "overwrite".

Review of the most recently received complaint, the "[redacted]" (**Exhibits Pjd-146/173**) finds an investigation report that was written for the first 3 complaints ([redacted], and [redacted]) received. At this time it was surmised the "probabilities" (probable root cause) for the 6 bottles missing a total of 58 tablets "[redacted]" or "[redacted]". The extra tablets might have jumped into the bottles over the brush that controls the tablets flow on the slats or human error when operator was adding extra tablets. The following is a summary of the complaints received for lot 80311:

Complaint #	Related DQRS #	Reason for the complaint
[redacted]		bottles short 15, 6, 9, 18, 1, and 9 tablets
[redacted]		one bottle contained 1 extra tablet
[redacted]		one bottle contained 1 extra tablet
[redacted]		bottles (2) short 1 and 5 tablets
[redacted]		20 bottles with discrepancy of 3 or more tablets (over or under) some were as many as 9
[redacted]		3 bottles short 1-3 tablets
[redacted]		bottle 19 short
[redacted]		bottle 15 short
[redacted]	[redacted]	bottles (2) short 45 and 75 tablets
[redacted]		bottle 19 tablets short
[redacted]		bottles (4) short 1, 1, 4, and 4 tablets

Discussion with Management:

We were told a change has been implemented to document anything out of the norm. The new SOP will be included with the response to this observation.

OBSERVATION 4

The persons performing and double-checking the cleaning and maintenance are not dating and signing or initialing the equipment cleaning and use log.

a. On 12/12/08, review of the Line (b)(Maintenance Use and Cleaning Record noted the clean-up of this area, last used 12/11/08, was not documented on this log or on the Cleaning and Washroom Area log where "(b) (4) cleaning of the various rooms are documented. The area referred to as Line F was clean with no sign of "inspection" activities for the lot of Metformin, (b) (4) that was inprocess on 12/8-11/08. Inspection of Lot (b) (4) was not complete.

b. Failure to document (b) (4) cleaning between packaging of Atenolol Tablet lot (b) (4) and Tramadol HCl tablet lot (b) (4) both packaged on Line (b)(on 10/31/08. Tramadol lot (b) (4) was ultimately inspected for the presence of Atenolol following the discovery of Atenolol Tablet(s) in the packaging room after packaging the Tramadol lot.

Reference: 21 CFR 211.182

Supporting Evidence and Relevance:
4.a.

Line (b)(Maintenance Use and Cleaning Records dating from 5/19/08 – 12/11/08 is attached as **Exhibits Pjd-174/180**. The last page (**Exhibit Pjd-180**) documents Metformin HCL lot (b) (4) was in this area, reportedly being inspected, from 12/8-11/08. The next entry on this log is "OUT OF SERVICE" and this entry is dated 12/12/08. There is no indication in this log that the room/area was cleaned but when we visited it on 12/12/08 there was no obvious evidence that the area was being used for tablet inspection. However, in this area there were 5 tables pushed up against the walls and 15 chairs stacked and pushed up against the wall. There was a pallet of white paper, approximately the size of the table tops, and an Induction sealer, Caraco Asset #(b) (4).
An additional entry on this log was made on 12/22/08 which states "(b) (4) [redacted]" (**Exhibit Pjd-179**). "Line (b)(" was located in a big open area, not inside a room.
The Maintenance Use and Cleaning Record for the CLEANING AND WASHROOM AREA (**Exhibits Pjd-181/182**) does not have an entry for Metformin HCl lot (b) (4) that had been in Area (b)(. I was told the inspection of lot (b) (4) as instructed in SPO (b) (4) (**Exhibit Pjd-183**) was not completed when it was stopped. SOP (b) (4) "(b) (4) [redacted]" requires cleaning operations to be documented in the log. It was through my review of this cleaning and washroom area log that I discovered Line (b)(existed. We had been told Line (b)(inspection room was where the (b) (4) inspections were performed.

4.b.

The maintenance use and cleaning record (MUCR) documents the Tramadol HCL following the Atenolol on 10/31/08 but no record exists of a "(b) (4)" clean in between lots (**Exhibit #JRL 10**). The firm annotated between MUCR entries the following comment, "(b) (4) ." The comment or the (b) (4) clean referenced was neither dated nor signed.

Discussion with Management:

At one time during Patsy Domingo's reading of line 4a, Mr. Ajac-Ayodele stated "(b) (4) ".

Additionally, relating to our problems with Area (b) (4) Mr. Ajac-Ayodele replied "(b) (4) "

Mr. Ajac-Ayodele said he had no objections to the findings and was aware of the issue. Further comments and/or corrective actions to this observation will follow in the written response.

OBSERVATION 5

Written records of major equipment cleaning, maintenance, and use are not included in individual equipment logs.

Induction sealer, Caraco asset # (b) (4), located in "Line (b) (4) " area does not have a usage log. This moveable equipment was utilized for unsealing and sealing finished product containers subjected to inspection for various reasons as assigned by the Quality Unit via a Special Processing Operation (SPO) order.

Reference: 21 CFR 211.182

Supporting Evidence and Relevance:
This sealer was observed in the Line (b) (4) area on 12/12/08. This sealer had a Caraco Asset # (b) (4) assigned to it. The Maintenance Use and Cleaning log for Line (b) (4) (Exhibit 180) did not contain information regarding use of this piece of equipment for the various inspection operations conducted.

Discussion with Management:

In response to our issue with Area [redacted], Mr. Ajac-Ayodele replied "T(b) (4) [redacted]"

The attendees explained they would not be using equipment that is not dedicated to a line in the future. This was in reference to the induction sealer mentioned in this observation.

REFUSALS

No refusals were encountered during the inspection.

GENERAL DISCUSSION WITH MANAGEMENT

Explained they would only be conducting these SPOs on the packaging lines and in the two processing rooms, one of which holds an automated tablet checker which was being qualified during our inspection. Management indicated they would have two dedicated people who set up equipment and train all others, but Patsy indicated this was supposedly instituted already as a result of an earlier 2008 inspection at the Detroit Caraco facility. Management informed us that all operators were newly trained to make note of processing anomalies such as that which we witnessed where tablets were spilling on the floor (yet no note was made in the packaging record). They said no more equipment, such as the induction sealer, will be used that is not part of a dedicated line.

ADDITIONAL INFORMATION

None

SAMPLES COLLECTED

None

VOLUNTARY CORRECTIONS

During this inspection, two verbal concerns noted during the previous 3/2008 inspection were verified for corrective action. The firm no longer conducts the hand filling of bottles during the packaging process and this practice has not been used since 4/2008. No occurrences were observed

during the current inspection. Packaging records were reviewed for actual yields of product and it was verified that the firm issued a new form, No. (b) (4) Rev No. (b) (4) (04/01/08), to calculate the percentages of actual and theoretical yields for packaging runs. All concerns from the previous inspection were corrected in April 2008.

EXHIBITS COLLECTED

Pjd-1/15	Listing of Special Processing Operations (SPO's) 101/07 – present
Pjd-16/19	SOP (b) (4) "(b) (4) (SPO's)"
Pjd-20/21	Organization Chart
Pjd-22/35	Documents pertaining to Meloxicam Tablet lot (b) (4)
Pjd-36/103	Documents pertaining to Tramadol Hydrochloride Tablet lot (b) (4)
Pjd-104/114	Documents pertaining to Metformin HCl tablet lot (b) (4)
Pjd-115/127	Documents pertaining to Zolpidem Tartrate Tablets lot (b) (4)
Pjd-128/134	Packaging Record for Zolpidem Tartrate lot (b) (4)
Pjd-135/145	Packaging Record for Zolpidem Tartrate lot 80311A
Pjd-146/173	Complaint (b) (4) for Zolpidem lot 80311A
Pjd-174/179	Maintenance Use and Cleaning Record for Line (b)(
Pjd-180	Last page of Line (b)(log, collected on 12/12/08
Pjd-181/182	Maintenance Use and Cleaning Record for Cleaning and Washroom Area
Pjd-183	SPO #(b) (4) for Metformin HCl 1000 mg lot (b) (4)
Pjd-184/185	SPO #(b) (4) and Inspection Report for Clonazepam Tablet lot (b) (4)
Pjd-186/214	Complaint (b) (4) dated 9/30/08 for Clonazepam Tablet lot (b) (4)
AJW 1/57	Full packaging record for lot (b) (4)
AJW 58/80	Investigation report IR-(b) (4) relating to lots (b) (4) (b) (4) (b) (4) (b) (4)
AJW 81/82	Cover sheet and label sheet from packaging record for lot (b) (4)
AJW 83/84	Cover sheet and label sheet from packaging record for lot (b) (4)
AJW 85	SPO-(b) (4) conducted on lot (b) (4)
AJW 86/87	Maintenance, Use and Cleaning record for line (b)(8/14-22/08
AJW 88/91	Cover sheet, incident tracking sheets, and SPO from packaging record (b) (4)
AJW 92	Lot (b) (4) packaging record Cover sheet
AJW 93	Lot (b) (4) packaging record yield calculations
AJW 94	Lot (b) (4) packaging record packaging supply master document
AJW 95	Lot (b) (4) packaging record material transfer form

AJW 96 Lot (b) (4) packaging record copy of bulk label
AJW 97 Lot (b) (4) packaging record QA hold tracking sheet
AJW 98 Lot (b) (4) packaging record SPO
AJW 99 Lo (b) (4) packaging record Material Transfer Form
AJW 100/101 Lot (b) (4), Cover sheet and SPO due to embedded latex
AJW 102 Lot (b) (4) Packaging record cover sheet
AJW 103 Lot (b) (4) Sample outsert
AJW 104 Lot (b) (4) Yield calculation
AJW 105 Lot (b) (4) SPO for foreign tablet
AJW 106 Lot (b) (4) QA Hold Initiation
AJW 107 Lot (b) (4) Incident Tracking sheet
AJW 108 Lot (b) (4) Packaging line release checklist
AJW 109-110 IR (b) (4) summary relating to Lot (b) (4)
AJW 111 written line record included with IR (b) (4)

JRL-1 Incident Tracking Sheet #IR (b) (4) regarding foreign tablets discovered after Packaging
JRL-2 Packaging Line Release Checklist for Methimazole tablets lot# (b) (4)
JRL-3/4 Investigation Report for IR (b) (4)
JRL-5/6 Email memo regarding foreign tablet discovery
JRL-7 Special Processing Operation (SPO) (b) (4) for (b) (4) inspection of lot (b) (4)
JRL-8 Incident Tracking Sheet #IR (b) (4) regarding foreign tablets discovered during Packaging
JRL-9 Investigation Report for IR (b) (4)
JRL-10 Maintenance Use and Cleaning Log 10/25-11/3/2008

ATTACHMENTS

#1 EES assignment ANDA (b) (4)
#2 EES assignment ANDA (b) (4)
#3 EES assignment ANDA (b) (4) Pantoprazole Sodium 20 mg & 40 mg Delayed Release Tablets
#4 EES assignment ANDA (b) (4) Gabapentin 100 mg, 300mg, & 400 mg capsules
#5 EES assignment ANDA (b) (4)

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